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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,211	10/31/2001	Jeffrey L. Browning	A013 US CON	6970

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,211	BROWNING ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51,53,55-57,59 and 60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51,53,55-57,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Browning *et al*

1. The amendment filed 3/10/2005 is acknowledged and entered into the record. Accordingly, claims 1-50,52,54, and 58 are canceled without prejudice or disclaimer, and claims 5- and 60 are newly added.

2. Claims 51,53,55-57, and 59-60 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

4. The disclosure is objected to because of the following informalities:

a. The drawings (i.e. figure 1) must be corrected to include a sequence identifier. MPEP 2422.02 indicates that *"when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings."*

Appropriate correction is required.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

5. The rejection of claims 51,53,55,56, and 57 under 35 USC § 112, 1st paragraph as lacking written description is maintained for the reasons of record. Applicant argues

that the instant specification has provided sufficient support to identify the composition of the claimed agents. Specifically applicant argues that the soluble LTβR agent is to contain at least one ligand binding domain of LTβR. Applicant indicates that the specification teaches means of making the soluble LTβR and also indicates that any or all functional portions of the LTβR ligand binding domain are taught. Applicant additionally contends that the specification discloses working examples of how to synthesize LTβR soluble domains and means of using the soluble LTβR domains (i.e. examples 1-7). Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

The specification of the instant application teaches generically that soluble LTβR domains are effective at modulating humoral immune responses such as treating systemic lupus erythematosus (SLE). Specifically, the specification teaches that LTβR of SEQ ID No: 1 (i.e. the extracellular domain of LTβR) is critical for this type of modulation or treatment. However, what the specification does not show is the breadth of the claimed invention (i.e. the use of any soluble LTβR, such as fragments of the extracellular domain). The specification does not show which portion of the soluble LTβR extracellular domain is critical for this function by means of a core structure or motif that is representative of the entire genus of soluble LTβR. The specification has only taught SEQ ID No: 1 and no other and therefore the single species of SEQ ID No: 1 is insufficient to support the breadth of the genus encompassed by the claims. Moreover, since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "soluble LTβR", the disclosure of a single species

is insufficient to teach the genus of soluble LTβR claimed.

Applicant additionally contends that given the state of the art and the teachings of the specification, one of skill in the art would readily recognize that applicant was in possession of the entire breadth of the genus claimed. Specifically, applicant argues that because SEQ ID No: 1 was present and taught in the specification, one of skilled in the art could easily recognize Applicant's possession of all possible soluble forms of LTβR. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejections of record. Specifically, applicant is relying on the general knowledge and skill in the art to describe the omitted information concerning the soluble portions of LTβR, however, this is insufficient because it is specific not general guidance that is needed. Since the specification fails to describe the common attributes and or characteristics that identify the members of the genus, the disclosure of SEQ ID No: 1 alone is insufficient to describe the genus of soluble LTβR claimed.

Lastly, applicant contends that all possible species represented by a genus need not be disclosed if a representative number of species be disclosed. Applicant additionally contends that the disclosure of two working examples of soluble LTβR is sufficient to describe the scope of the instantly claimed invention. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. The working examples (i.e. example 1 and 2) teach the expression of human and murine soluble LTβR. Although these are two species of the LTβR, it does not support the breadth of all possible soluble LTβR, encompassed by the claims (i.e. fragments of LTβR, for example). The Guidelines for the Examination of

Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3). Such is the case of the instantly claimed invention. The specification teaches SEQ ID No: 1 but claims any and all possible soluble LTβR ligand binding domains. No relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics have been disclosed.

In the absence of structural characteristics that are shared by members of the genus of "soluble LTβR comprising the ligand binding portion" or "functional fragment" of SEQ ID No: 1, the skilled artisan would conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol.

66, No. 4, pages 1099-1111, Friday January 5, 2001.

Therefore, the rejection of claims under 35 USC 112, 1st paragraph is newly applied and maintained for the reasons of record.

It is noted that applicant's arguments concerning the written description concerning the heterologous protein domains is deemed persuasive.

Claim Rejections Maintained - Obvious Type Double Patenting

6. The rejection of claims 51,53, and 55-57 under the judicially created doctrine of obvious type double patenting as being obvious over US Patent 6,403,087 (herein `087) and US Patent 6,669,941 (herein `941) is maintained for the reasons of record. Applicant argues that the claims of the issued patents encompass methods of treating Th1 related diseases (`087) and method of treating Th1 related autoimmune diseases (`941) comprising the administration of a soluble LTβR, while the claims of the instant invention are drawn to a method of treating Th2 related diseases comprising the administration of a soluble LTβR. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. Specifically, the claims encompass the administration of what appears to be the same product (i.e. a soluble LTβR). Because the product used for administration of each of the patented cases and in the instant invention appears to be the same product, inherently it would accomplish the same function and therefore, not patentably distinct.

Therefore, the rejection under the judicially created doctrine of obvious type double patenting is maintained for the reasons of record.

New Arguments

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 51,53, and 55-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating SLE comprising the administration of a soluble LTβR of SEQ ID No: 1 fused to an immunoglobulin (IgG1) Fc domain, wherein the soluble LTβR of SEQ ID No: 1 IgG1 Fc domain complex specifically elicits a specific humoral response, does not reasonably provide enablement for a method of treating SLE comprising the administration of any and all fragments or functional sequence of soluble LTβR fused to any heterologous protein domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQZd 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of treating a SLE comprising the administration of a soluble LTβR fused to a heterologous protein domain. The invention

is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims of the instant invention read on the administration of any portion of the soluble or extracellular domain of LTβR fused to any heterologous protein.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of soluble portion of the polypeptide that is used for the elicitation of the humoral immune response.It would require significant study to determine which regions of the extracellular domain or soluble portion of LTβR that is capable of treating SLE, and identifying this portion is in itself an inventive and unpredictable undertaking in itself. This would require years of inventive effort, with each step not providing any guarantee of success .

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein chemistry. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single “lysine” reside at position 118 of acidic fibroblast growth factor by “glutamic acid” led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while

replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2).

Working examples

The working examples in the instant specification has only provided a soluble LTβR of SEQ ID No: 1 fused to a human IgG Fc domain and its effects in the elicitation of a humoral response (see example 7, in particular)

Guidance in the specification

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all fragments derived from the soluble portion of LTβR. .

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these

unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 51,53,55-57, and 59-60 are rejected under 35 U.S.C. 102(e) as being anticipated by Browning *et al* (US Patent 5,925,351). Browning *et al* teach a method comprising the administration of a soluble LTβR of SEQ ID No: 1 fused to a

heterologous protein domain, wherein the heterologous protein domain is an immunoglobulin Fc domain, wherein the administration is to a human (see col. 4 for example). While Browning *et al.* do specifically characterize soluble LTβR fragments are used for the treatment of SLE, the claimed functional limitation would be an inherent property of the soluble LTβR, because there does not appear to be a patentable distinction between the products of the claimed invention and that taught in the prior art. Moreover, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). Therefore, in the absence of evidence to the contrary, the burden is on the applicant to prove that the method of using the claimed soluble LTβR is different from that taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 3/10/2005.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
May 17, 2005